Memorandum

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Center for Drug Evaluation and Research

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TO: M. Dianne Murphy, M.D.
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Office of the Commissioner
and
Solomon Iyasu, M.D., M.P.H., Acting Deputy Director
Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatric Drug Development (OCTAP)

SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review Drug Use Data - Rapamune® (sirolimus) Oral Solution, NDA 21-083; Rapamune® (sirolimus) Tablets, NDA 21-110 tablets

****This document contains proprietary drug use data which cannot be shared outside of FDA without clearance from the data vendors obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for Rapamune® (sirolimus) in the pediatric population (ages 0-16 years) from December 1, 2002 through November 30, 2005, with a primary focus on patterns of use 12 months before and 12 months following the granting of Pediatric Exclusivity for Rapamune® on November 17, 2004. Data on other available oral immunosuppressive therapies were examined as well. Drug use data were derived from Verispan, LLC, Vector One®: National (VONA) and Total Patient Tracker (TPT) along with IMS Health, National Disease and Therapeutic Index. We used these data to estimate the number of prescriptions dispensed by retail pharmacies, the number of patients who received dispensed Rapamune® retail prescriptions, and the number of drug mentions by office-based physicians.

Results from our review show that there was an overall increase (5.7%) in the number of prescriptions dispensed for the seven oral immunosuppressive agents during the 3-year period. Dispensed prescriptions for Rapamune® increased by approximately 21% from the pre- to the post-exclusivity period. Rapamune® accounted for approximately 4.1% of the total dispensed prescriptions for the oral immunosuppressant market during the post-exclusivity period.

The top ranked prescribing specialty was nephrology accounting for one-quarter of the total dispensed prescriptions for Rapamune® while pediatrics accounted for approximately 3-4 % of the total prescriptions dispensed. Regarding indications for use, Rapamune® was commonly mentioned for "follow-up examination following other treatment" (ICD-9 code V67.5) during adult office-based physician-patient encounters. In office-based pediatric visits, "heart transplantation" (ICD-9 code V42.1) was also recorded.

The estimated number of pediatric patients that received a prescription for Rapamune® increased from 1,104 patients in the pre-exclusivity period to 1,471 patients during the post-exclusivity period and accounted for an average of 4.3% of all patients receiving Rapamune® over the three-year period of this analysis. The number of Rapamune® prescriptions dispensed to pediatric patients also increased during the same time period.

INTRODUCTION

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Rapamune® (sirolimus) is an oral immunosuppressive agent indicated for the prophylaxis of organ rejection in patients aged 13 years or order receiving renal transplants. Rapamune® (sirolimus) Oral Solution (NDA 21-083) was approved on September 15, 1999, and Rapamune® (sirolimus) Tablets (NDA 21-110) was approved on August 25, 2000. The solution is available at a concentration of 1 mg/mL, and the tablets are available as 1 mg and 2 mg triangular-shaped tablets.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Rapamune® on November 17, 2004, under NDA 21-083/S-019 and NDA 21-110/S-024.

This review describes outpatient drug usage of Rapamune® (sirolimus) in the pediatric population as compared to the adult population two years before and one year after (with a primary focus patterns of use 12 months before and 12 months following) the granting of pediatric exclusivity. The utilization of Rapamune® is provided in the context of other oral drug

products routinely used in the prophylaxis of organ rejection. These products include azathioprine and cyclosporine, as well as other products in the immunosuppressant drug class.

METHODS

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail in the Appendix.

IMS Health, National Sales Perspectives data (see Appendix) were used to determine the setting in which Rapamune® is sold and distributed. Sales of this product by number of tablets and volume (mL) sold from the manufacturer to retail and non-retail channels of distribution were analyzed for the three 12-month periods from December 2002 through November 2005 (Table 1). From these data, it is clear that this product is sold primarily to ambulatory settings. Over 56% of all Rapamune® sales are into the retail channels and 28% are into mail order channels.

Table 1: Total Number of Rapamune® Tablets and mL Combined (in thousands) Sold to U.S. Distribution Channels During December 1, 2002 through November 30, 2005

	Dec 2002 – Nov 2003		Dec 2003 – Nov 2004		Dec 2004 - Nov 2005	
	N	***%***	**N**	***%***	**N**	***%***
Retail*	10,558	*52.4*	12,707	*53.6*	14,489	*55.5*
Non-Retail**	4,184	*20.8*	4,506	*19.0*	4,289	*16.4*
Mail Order and Other***	5,400	*26.8*	6,501	*27.4*	7,349	*28.1*

**Retail includes chain, independent, and food store with pharmacies.*
***Non-Retail includes long term care, non-federal hospitals, federal facilities, clinics, HMO's, home health care.*
**** Other includes prisons, universities, and other.*
Source: IMS Health, IMS National Sales Perspectives Combined, MAT Dec2002 – Nov 2005. Data Extracted January 2006. (Original file: 0601ser1.dvr)

Because the bulk of drug product sales of Rapamune® for this time period were to outpatient settings, we focused our analysis only on the outpatient setting. We examined the utilization patterns for Rapamune® and other oral immunosuppressive therapies used in the prophylaxis of organ rejection. Six other oral immunosuppressive drug substances (USC 86100 **)** are included in this analysis: azathioprine, mycophenolate mofetil, tacrolimus anhydrous, cyclosporine, cyclosporine microemulsion, and mycophenolate sodium.

Outpatient drug use patterns were derived from Verispan, LLC, Vector One®: National (VONA) and Total Patient Tracker (TPT) along with IMS Health, National Disease and Therapeutic Index (see Appendix). Estimates of the number of prescriptions dispensed by retail pharmacies, the number of patients who received dispensed Rapamune® retail prescriptions, and the number of drug mentions by office-based physicians were obtained. Outpatient drug utilization patterns were examined for the 3-year period from December 1, 2002 through November 30, 2005.

RESULTS

I. Dispensed Prescriptions

All immunosuppressants: There was an overall increase in the number of prescriptions dispensed for the seven immunosuppressive drugs during the 3-year period from December 1, 2002 through November 30, 2005. (Table 2). During the pre-exclusivity period (December 2003 to November 2004), approximately 3.8 million prescriptions were dispensed for these oral immunosuppressant drug products. During the post-exclusivity period (December 2004 to November 2005), approximately 4.0 million prescriptions were dispensed, representing an increase of approximately 5.7%.

Rapamune® (sirolimus): During these two 12-month time periods, dispensed prescriptions for Rapamune® increased by approximately 21%, from over 136,000 prescriptions during the pre-exclusivity period to almost 165,000 prescriptions during the post-exclusivity period. With respect to the overall immunosuppressant market, Rapamune® accounted for approximately 4.1% of the total dispensed prescriptions during the post-exclusivity period.

Table 2: Total Number of Prescriptions† Dispensed in Retail Pharmacies Nationwide for Oral Immunosuppressant Drug Products During December 2002 – November 2005

	Dec 2002 – Nov 2003		Dec 2003 – Nov 2004		Dec 2004 – Nov 2005	
	TRxs N	Share %	TRxs N	*Share %*	TRxs N	*Share %*
Transplant/Immunosuppressants	**3,602,400**	***100.0%***	**3,826,594**	***100.0%***	**4,043,087**	***100.0%***
Azathioprine	1,295,672	*36.0%*	1,308,998	*34.2%*	1,405,859	*34..8%*
Mycophenolate mofetil	702,624	*19.5%*	814,333	*21.3%*	883,092	*21.8%*
Tacrolimus anhydrous	609,008	*16.9%*	706,151	*18.5%*	781,464	*19.3%*
Cyclosporine	757,994	*21.0%*	727,301	*19.0%*	647,816	*16.0%*
Sirolimus	106,773	*3.0%*	136,415	*3.6%*	164,984	*4.1%*
Rapamune®	106,773	*100.0%*	136,415	*100.0%*	164,984	*100.0%*
0-16	3,499	*3.3%*	4,891	*3.6%*	7,113	*4.3%*
17+	103,082	*96.5%*	130,804	*95.9%*	156,800	*95.0%*
UNSPEC.	192	*0.2%*	720	*0.5%*	1,071	*0.6%*
Cyclosporine microemulsion	130,329	*3.6%*	128,362	*3.4%*	130,146	*3.2%*
Mycophenolate sodium	--	--	5,034	*0.1%*	29,726	*0.7%*

Verispan, LLC, December 2002 – November 2005, Data Extracted 1/06 (File: VONA A060063 1-30-06 Rapamune Oral Age.qry)
† Totals and subtotals may not sum exactly due to rounding

II. Prescribing Specialty

The nephrology specialty consistently accounted for 25% to 28% of the total dispensed prescriptions for Rapamune® during the three 12-month time periods surveyed (Table 3). During

the same three-year period, pediatrics accounted for approximately 3-4 % of the total prescriptions dispensed.

Table 3: Total Number of Prescriptions† Dispensed in Retail Pharmacies Nationwide for Rapamune® by Physician Specialty During December 2002 – November 2005

		Dec 2002 – Nov 2003		Dec 2003 – Nov 2004		Dec 2004 – Nov 2005	
		TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
Rank	Specialty	N	*%*	N	*%*	N	*%*
	Total	**107,886**	***100.0%***	**142,825**	***100.0%***	**164,972**	***100.0%***
1	**Nephrology**	27,305	*25.3%*	38,041	*26.6%*	45,785	*27.8%*
2	**Unspecified**	18,776	*17.4%*	20,752	*14.5%*	23,529	*14.3%*
3	**General Surgery**	17,005	*15.8%*	22,836	*16.0%*	23,370	*14.2%*
4	**Internal Medicine**	9,233	*8.6%*	13,778	*9.6%*	16,123	*9.8%*
5	**All Other Surgery**	6,048	*5.6%*	6,340	*4.4%*	9,829	*6.0%*
6	**Cardiology**	4,272	*4.0%*	6,996	*4.9%*	8,758	*5.3%*
7	**Pediatrics**	3,060	*2.8%*	4,093	*2.9%*	6,518	*4.0%*
8	**Hospital**	4,541	*4.2%*	5,962	*4.2%*	5,385	*3.3%*
9	**Gastroenterology**	3,310	*3.1%*	5,045	*3.5%*	5,294	*3.2%*
10	**Other**	3,932	*3.6%*	4,536	*3.2%*	3,917	*2.4%*
	All Others (36)	10,404	*9.6%*	14,446	*10.1%*	16,464	*10.0%*

Verispan, LLC, December 2002 – November 2005, Data Extracted 1/06 (File: VONA A060063 1-24-06 Rapamune MD.qry)
† Totals and subtotals may not sum exactly due to rounding

III. Patient Demographics

Prescriptions dispensed to pediatric patients (age 0-16 years) for Rapamune® increased from almost 5,000 prescriptions during the pre-exclusivity period to over 7,000 prescriptions during the post-exclusivity period (Table 4). On average, dispensed prescriptions for children (ages 0-16 years) accounted for approximately 6.0% of the entire dispensed prescriptions in the oral immunosuppressant market during the post-exclusivity period (data not shown). This was a slight increase from 5.6% during the pre-exclusivity period (data not shown).

Children aged 12-16 years accounted for over half of the Rapamune® prescriptions dispensed to the pediatric age group during the pre- and post-exclusivity periods, with 55.4% (2,712 prescriptions) and 58.7% (4,174 prescriptions), respectively.

Table 4. Number and Percentage of Rapamune® Prescriptions† Dispensed to Adult and Pediatric Patients by Retail Pharmacies During December 2002 – November 2005.

	Dec 2002 – Nov 2003		Dec 2003 – Nov 2004		Dec 2004 – Nov 2005	
	TRxs	***Share***	**TRxs**	***Share***	**TRxs**	***Share***
	N	***%***	**N**	***%***	**N**	***%***
Rapamune®	**106,773**	***100.0%***	**136,415**	***100.0%***	**164,984**	***100.0%***
Age 0-16	**3,499**	***3.2%***	**4,891**	***3.6%***	**7,113**	***4.3%***
0-1	37	*1.1%*	41	*0.8%*	42	*0.6%*
2-11	1,816	*51.9%*	2,138	*43.7%*	2,897	*40.7%*
12-16	1,646	*47.0%*	2,712	*55.4%*	4,174	*58.7%*
Age 17+	**103,082**	***96.5%***	**130,804**	***95.9%***	**156,800**	***95.0%***
Age Unspecified	**192**	***0.2%***	**720**	***0.5%***	**1,071**	***0.6%***

Verispan, LLC, December 2002 – November 2005, Data Extracted 1/06 (File: VONA A060063 1-31-06 Rapamune Age.qry)
† Totals and subtotals may not sum exactly due to rounding

According to data from Verispan's Total Patient Tracker, the estimated number of patients receiving prescriptions for Rapamune® has increased approximately 10.7% from the pre-exclusivity period (December 2003 – November 2004) to the post-exclusivity period (December 2004 – November 2005) (Table 5). Similar to dispensed prescription data, the number of pediatric patients ages 0-17 years that received a prescription for Rapamune® accounted for an average of 4.3% of all patients receiving Rapamune® over the three-year period of this analysis.

Table 5. The Estimated Number of Unique Patients Receiving a Prescription for Rapamune® From Retail Pharmacies During December 2002 – November 2005

	Dec 2002 – Nov 2003		Dec 2003 – Nov 2004		Dec 2004 – Nov 2005	
Age Groups	**Projected Patient Count**	***%***	**Projected Patient Count**	***%***	**Projected Patient Count**	***%***
Total	23,100		27,083		29,985	
Age 0-17	925	*4.0%*	1,104	*4.1%*	1,471	*4.9%*
Age 17+	23,715	*102.7%*	27,779	*102.6%*	30,906	*103.1%*

Verispan, LLC, Total Patient Tracker, December 2002 - November 2005, Data Extracted 2-7-06
(File: TPT Governale 2-7-06 Rapamune Age Group Report Display Time.xls)
†Subtotals may not sum exactly due to rounding error and patients aging in the course of the study period.

IV. Indications for Use

The most common situation where Rapamune® was mentioned for adults during office-based physician-patient encounters was "follow-up examination following other treatment" (ICD-9 code V67.5) throughout the time period surveyed (Table 6). In the pediatric population, "heart transplantation" (ICD-9 code V42.1) was also recorded during a patient visit to an office-based physician practice.

Table 6: Indications Associated with Mentions of Rapamune® (in thousands) During Office-Based Physician Visits by Patient Age Groups During December 1, 2002 through November 30, 2005

	Dec 2002 – Nov 2003		Dec 2003 – Nov 2004		Dec 2004 – Nov 2005	
	N (000)	%	N (000)	%	N (000)	%
RAPAMUNE® WYE 99/09	**35**	***100.0%***	**108**	***100.0%***	**45**	***100.0%***
Patient Age 17+	33	*95.5%*	106	*98.5%*	42	*93.5%*
V67.5 Follow-up examination following other treatment	20	*60.7%*	106	*100.0%*	22	*53.0%*
799.9 Other unknown and unspecified cause	---	---	---	---	10	*23.5%*
996.8 Complications of transplanted organ	6	*17.1%*	---	---	10	*23.5%*
V42.0 Kidney transplant	7	*22.2%*	---	---	---	---
Patient Age 0-16	2	*4.5%*	2	*1.5%*	3	*6.5%*
V67.5 Follow-up examination following other treatment	---	---	2	*100.0%*	3	*100.0%*
V42.1 Heart transplant	2	*100.0%*	---	---	---	---

Source: IMS Health, National Disease and Therapeutic Index™, MAT Nov 2003 – Nov 2005, Extracted Jan06.
Original File 0601Rapamune AgDx.dvf

DISCUSSION

According to the Organ Procurement and Transplantation Network, approximately 13,781 kidney transplants were performed during year 2005[1]. This figure was down from the previous year's estimate of 16,004 kidney transplants. The number of pediatric kidney transplants (ages <1 year to 17 years) was approximately 718 or 5% of the total renal transplants for all ages. The age 11-17 year category represented approximately 63% of the renal transplants for the pediatric age group. These figures are consistent with the demographic figures obtained from the analysis of dispensed prescriptions in this consult.

According to the United States Renal Data System 2005 Annual Data Report, the most common immunosuppressive regimen reported for transplanted patients during years 2000 – 2003 was a combination of tacrolimus and mycophenolate mofetil, with steroids.[2] Result from this review have shown that Rapamune® accounted for less than 5% of all seven immunosuppressive prescriptions dispensed during the 3-year period.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated the settings in which Rapamune® was mostly used based on the IMS Health, National Sales Perspectives™. These data do not provide a direct estimate of use but only provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use. While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, use outside of the retail pharmacy settings was not captured in our analysis.

[1] OTPN: Organ Procurement and Transplantation Network [on line]. Available from URL: http://www.optn.org/latestData/rptData.asp/ (Accessed 2006 February 1).
[2] U.S. Renal Data System. 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States [on-line]. Available from URL: http://www.usrds.org/ (Accessed 2006 January 31).

Throughout our analysis, we used the agency's cut-off age definition of a pediatric patient (age 0-16 years), except when we use Verispan's Total Patient Tracker tool for providing estimates of the total number of unique patients receiving prescriptions for Rapamune®. Age bands available through this data resource with an age break at age 17 years are fixed and cannot yet be customized to reflect the agency's definition. In addition, using this tool does not allow summary of age bands in each time period, due to patient aging in the course of the study period.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not common in the pediatric population, as in the case of Rapamune®.

CONCLUSION

For all age groups, prescriptions for Rapamune® (sirolimus) increased by approximately 20.9%, from over 136,000 prescriptions during the pre-exclusivity period to almost 165,000 prescriptions during the post-exclusivity period. In comparison to the overall market, Rapamune® (sirolimus) accounted for approximately 4.1% of the total dispensed prescriptions for the oral immunosuppressant market during the post-exclusivity period. The use of Rapamune® (sirolimus) is mostly in adult patients, with 0-16 year olds accounting for less than 5% of the overall outpatient usage during the 36-month study period. Similar to dispensed prescription data, the number of pediatric patients ages 0-17 years that received a prescription for Rapamune® accounted for an average of 4.3% of all patients receiving Rapamune® over the three-year period of this analysis. Patients in the 12-16 year old subgroup accounted for the majority of prescriptions dispensed to pediatrics in the post-exclusivity period, with almost 60% of the annual Rapamune® prescriptions dispensed to this group of pediatric patients. Nephrologists were consistently responsible for 25% to 28% of the total dispensed prescriptions for Rapamune® during the three 12-month time periods surveyed. During the same three-year period, pediatricians accounted for approximately 3-4 % of the total prescriptions dispensed.

APPENDIX

IMS HEALTH, IMS NATIONAL SALES PERSPECTIVES™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. IMS Health, National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, vials, and market share. These data are based on national projections.

For this analysis, the sales trend for Rapamune® (sirolimus) was examined from December 1, 2002 – November 30, 2005 inclusive.

Verispan, LLC; Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.8 billion prescription claims, representing over 160 million patients tracked across time.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Data for this analysis include prescriptions dispensed for Rapamune® (sirolimus) and other oral immunosuppressive agents from December 1, 2002 – November 30, 2005 inclusive.

Verispan, LLC; Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 1.8 billion prescription claims per year, which represents over 160 million patients tracked across time.

Data for this analysis include prescriptions dispensed for Rapamune® (sirolimus) and other oral immunosuppressive agents from December 1, 2002 – November 30, 2005 inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental U.S. The data are collected from a panel of roughly 2,000 – 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned and treatment patterns. The data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of Rapamune® during office-based physician visits during the time period December 1, 2002 – November 30, 2005 inclusive.

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